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Commensal bacteria at the interface of host metabolism and the immune system

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Abstract

The mammalian gastrointestinal tract, the site of digestion and nutrient absorption, harbors trillions of beneficial commensal microbes from all three domains of life. Commensal bacteria, in particular, are key participants in the digestion of food, and are responsible for the extraction and synthesis of nutrients and other metabolites that are essential for the maintenance of mammalian health. Many of these nutrients and metabolites derived from commensal bacteria have been implicated in the development, homeostasis and function of the immune system, suggesting that commensal bacteria may influence host immunity via nutrient- and metabolite-dependent mechanisms. Here we review the current knowledge of how commensal bacteria regulate the production and bioavailability of immunomodulatory, diet-dependent nutrients and metabolites and discuss how these commensal bacteria-derived products may regulate the development and function of the mammalian immune system.

The mammalian gastrointestinal tract harbors trillions of beneficial commensal bacteria, a population composed of at least 1,000–5,000 species[1,2]. Across the animal kingdom, species as diverse as flies, fish, mice and humans have co-opted the faculties of beneficial microbes to support normal development and homeostasis[3-14]. Recent studies have highlighted that alterations in the composition of commensal bacterial populations are linked to multiple metabolic and inflammatory diseases in humans including but not limited to inflammatory bowel disease (IBD), obesity, type 2 diabetes, atherosclerosis, allergy and colon cancer[9-15]. These associations provoke fundamental questions regarding the cellular and molecular pathways through which commensal bacteria regulate mammalian gene expression and influence resistance or susceptibility to a broad range of clinically important diseases.

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Recent studies have identified a critical role for commensal bacteria and their products in regulating the development, homeostasis and function of innate and adaptive immune cells[15-24]. Several recent comprehensive reviews have described how commensal bacteria are recognized by the innate immune system and how individual species or consortia of commensal bacterial species can influence distinct modules of the innate and adaptive immune response[15-24]. However, an emerging area that has received relatively little attention is how metabolites and nutrients derived from commensal bacteria regulate the host immune system.

Commensal bacteria are key regulators of digestion, a process that begins in the mouth and continues as ingested food and its digestive intermediates transit more than 20 feet (6 meters) to the end of the adult human gastrointestinal tract. Along the way, the digestive slurry is mixed with commensal bacteria, which are important for the extraction, synthesis and absorption of many nutrients and metabolites (Box 1), including bile acids, lipids, amino acids, vitamins and short-chain fatty acids (SCFAs; **Fig. 1a**). These nutrients and metabolites derived from commensal bacteria are directly linked to diet and digestion and are therefore considered to be diet-dependent microbial products (Box 1)[14]. In addition to producing diet-dependent metabolites and nutrients, commensal bacteria can produce many different diet-independent microbial products, examples of which are lipopolysaccharide and peptidoglycan (Box 1)[11-14,23,24].

Nutrients and metabolites derived from commensal bacteria may regulate immune cells via indirect and direct mechanisms. Commensal bacteria-mediated alterations in the availability or use of energy substrates (for example, by modulating oxidation of glucose and fatty acids) may indirectly influence the development, homeostasis and function of immune cells[5,11-14,25-31], although direct experimental analyses of these interactions are limited at present. In addition, direct effects of metabolites can be mediated via metabolite-specific receptors that can activate signal-transduction pathways and transcriptional programs that control differentiation, proliferation, migration and effector function of immune cells. The roles of diet-independent microbial products in the regulation of immunity have been recently discussed elsewhere[15-24]; therefore in this Review, we will discuss how commensal bacteria-derived diet-dependent nutrients and metabolites regulate the host immune system (**Fig. 1b**). We describe how commensal bacteria can regulate the synthesis and/or availability of bile acids, SCFAs, vitamins, amino acids and fatty acids. In the context of each of these diet-dependent nutrients and metabolites, we discuss current knowledge of how these factors regulate the immune response in the context of health and disease.

Regulation of bile acids by commensal bacteria

Bile acids are a family of cholesterol-derived amphipathic molecules that solubilize dietary fat in the small intestine to support the digestion and absorption of fat and of fat-soluble vitamins. In addition to their roles in regulating digestion, bile acids act as signaling molecules that regulate metabolic homeostasis[32,33] and, as we will discuss below, immune cell homeostasis and function. Commensal bacteria participate in the synthesis of bile acids in two main ways (**Fig. 2a**). First, commensal bacteria convert primary bile acids (for example, cholic and chenodeoxycholic acids), which are synthesized *de novo* by the liver, into secondary bile acids (for example, deoxycholic, lithocholic and muricholic acids) through dehydration reactions[34]. Both primary and secondary bile acids are subsequently reabsorbed in the ileum and returned via portal circulation to the liver, where they are conjugated to glycine (in humans) or taurine (in mice)[34,35]. These covalent modifications increase the efficiency of reabsorption of bile acids in subsequent rounds of digestion[34]. Second, commensal bacteria deconjugate bile acids to re-derive the unconjugated forms[36,37]. The reabsorption of unconjugated bile acids is inefficient; therefore, deconjugation of bile acids mediated by commensal bacteria promotes the excretion and elimination of bile acids[32].

Highlighting the influence of commensal bacteria on the synthesis of bile acids, mice and rats reared in the absence of commensal bacteria or treated with oral broad-spectrum antibiotics have fewer secondary bile acids and more conjugated bile acids in the fecal matter, ileum lamina propria, liver, kidney, heart and plasma compared to conventionally reared counterparts[38-45]. Consistent with these observations, some human patients with IBD have intestinal dysbiosis (Box 1) that is associated with lower concentrations of secondary bile acids in the feces and periphery as well as more conjugated bile acids in the feces compared to healthy subjects[45]. Such data suggest that commensal bacteria appear to be intimately involved in generating an array of bile acids, and at least a subset of these bile acid metabolites derived from commensal bacteria gain access to enterohepatic and systemic circulation (**Fig. 2a**).

Bile acid regulation of immune cells

The role of commensal bacteria in the production of bile acids raises the question of whether bile acids derived from commensal bacteria are associated with regulation of the host immune system. Some bile acids can regulate the function of immune cells via the G protein–coupled bile acid receptor 1 (GPBAR1; also known as TGR5 and membrane-type receptor for bile acids, M-BAR) and the nuclear receptor subfamily 1, group H, member 4 (NR1H4; also known as farnesoid X receptor, FXR), both of which are highly expressed in monocytes and macrophages as well as other immune cell types[32,33]. In macrophages and monocytes, bile acid signaling via these receptors is linked to a common anti-inflammatory response involving the inhibition of NF-κB activity and repression of NF-κB–dependent transcription (**Fig. 2b**)[45-49]. Treatment of macrophages with the highly selective GPBAR1 agonist INT-777 (ref. 50) is associated with higher cellular concentrations of cAMP and activation of protein kinase A (PKA) and of cAMP-responsive element-binding protein (CREB)[49]. The cAMP-PKA-CREB pathway lowers STAT1 phosphorylation and NF-κB transcriptional activity[51-53]. Macrophages treated with INT-777 exhibit lower NF-κB binding to the nitric oxide synthase 2 (*Nos2*) promoter and attenuated induction of the proinflammatory cytokines tumor necrosis factor (TNF), interleukin 6 (IL-6) and IL-1β in response to lipopolysaccharide[48]. These effects of INT-777 were not observed in *Gpbar1*$^{-/-}$ macrophages, indicating that GPBAR1 was required for the anti-inflammatory effects of INT-777. Consistent with these findings, loss-of-function studies indicate that *Gpbar1*$^{-/-}$ mice exhibited exaggerated colitis in response to treatment of dextran sodium sulfate (DSS) and trinitrobenzene sulfonate (TNBS), two mouse models of intestinal damage and inflammation[54].

Similarly, treatment of intestinal lamina propria CD11b$^+$ cells with the NR1H4-selective agonist INT-747 was associated with a decrease in the expression of NF-κB–dependent genes *Tnf, Il6, Il1b, Ifng* and *Nos2* in response to treatment with lipopolysaccharide[46]. Treatment of wild-type mice exposed to DSS or TNBS with INT-747 was also associated with lower expression of IL-1β, IL-6 and monocyte chemotractant protein 1 (MCP-1) as well as lower colonic inflammation[55]. However, unlike bile acid–GPBAR1 pathway–dependent inhibition of NF-κB activity, NR1H4-mediated repression of NF-κB–dependent transcription appears to be regulated through stabilization of the nuclear receptor corepressor 1 (NCoR1) on NF-κB–responsive elements, thereby blocking access to NF-κB[46]. Although future studies are required, the anti-inflammatory properties of the bile acid–NR1H4 pathway are likely not specific to monocytes and macrophages, as NR1H4 is expressed in other immune cell types, including liver natural killer T (NKT) cells (**Fig. 2c**). For example, in liver NKT cells NR1H4 regulates the expression of osteopontin[56,57], a pleiotropic protein that regulates many cell types, an example of which is neutrophils. Compared to wild-type mice, NR1H4-deficient mice have more liver NKT cell–derived osteopontin and increased liver neutrophils in concanavalin A–induced hepatitis[56]. Moreover, natural secondary bile acids, which can bind both GPBAR1 and NR1H4 (ref. 33), also appear to have anti-inflammatory effects in nonimmune cells, as treatment of intestinal epithelial cell lines such as Caco-2 cells with deoxycholic acid or lithocholic acid abrogates IL-1β–induced expression of IL-8 (ref. 45). Although GPBAR1 and NR1H4 are not fully redundant, as evidenced by the spontaneous intestinal inflammation observed at steady state in *Nr1h4*$^{-/-}$ mice with functional GPBAR1 but not *Gpbar1*$^{-/-}$ mice with functional NR1H4 (refs. 46,54), the above-mentioned studies indicate that bile-acid signaling pathways have a common anti-inflammatory function involving inhibition of NF-κB.

Bile acids in health and disease

The role of commensal bacteria in the production of bile acids and the anti-inflammatory effects of bile acids in some cell types raise questions about whether bile acids derived from commensal bacteria might influence the functions of the immune system in diseases associated with dysbiosis. Such diseases include IBD[45,58,59], obesity[6,60-63], non-alcoholic fatty liver disease[64], type 2 diabetes[62,63,65], atherosclerosis[66,67], colon cancer[68], viral infection[69,70] and others (**Fig. 2d**). Here we will briefly discuss IBD and viral infection.

As reviewed above, bile acids appear to regulate the function of at least some immune cell types through GPBAR1 and NR1H4, both of which lead to the inhibition of NF-κB–dependent expression of proinflammatory genes. Mice lacking GPBAR1 or NR1H4 exhibit exaggerated colitis in models of intestinal inflammation, and stimulating these receptors appears to be associated with protection against colon tissue damage[46,54,55,71]. Patients with IBD, at least two diseases (Crohn's disease and ulcerative colitis) with diverse phenotypes, are reported to have alterations in commensal bacteria as well as diminished concentrations of bile acids[45,58,59] and, in the case of Crohn's disease, diminished NR1H4 activity in the ileum[72]. These correlative studies provoke speculation about whether loss of bile acids derived from commensal bacteria might contribute to the development of at least some subsets of IBD and whether the use of analogs of bile acids might be a novel therapeutic strategy to treat this complex set of diseases. However, the conjugated bile acid taurocholic acid supports the growth of pathogenic bacteria that promote colitis in IL-10–deficient mice[73], indicating that a better understanding of the commensal bacteria–bile acid–immune system axis is necessary to fully understand the role of bile acids in IBD. In this context, additional research will be necessary to investigate the possible roles of bile acid metabolites in clinically stratified IBD patients.

The bile acid–mediated decrease in NF-κB activity in macrophages and monocytes may also be associated with the impaired antiviral immunity observed in germ-free mice or mice with experimentally altered composition of commensal bacteria[69,70]. Macrophages from germ-free and antibiotic-treated mice have lower NF-κB–dependent gene expression and interferon responses in association with diminished $CD8^+$ T cell and NKT cell function, diminished capacity to limit viral replication and greater susceptibility to viral infection[69,70]. These studies suggest that commensal microbiota provide instructive tonic signals that support the proper functioning of innate immune cells and the coordination of adaptive immune responses[69,70]. It is also possible, however, that germ-free and antibiotic-treated mice have impaired macrophage and NKT function because of elevated bile acid concentrations, which would be expected to inhibit NF-κB–dependent gene expression, such as the interferon response programs in macrophages and monocytes. Consistent with this idea are studies demonstrating that cells treated with bile acids have an impaired capacity to limit replication of hepatitis C virus and of porcine enteric calicivirus[74,75]. In addition, treatment of hepatocytes with the NR1H4 antagonist Z-guggulsterone improves the ability of hepatocytes treated with bile acids to limit replication of hepatitis C virus[75]. This bile acid–mediated effect is associated with activation of the PKA pathway and less STAT1 phosphorylation as well as impaired interferon responses[74]. Collectively, these studies suggest that an increase in bile acid signaling via GPBAR1 and NR1H4 may be associated with lower antiviral immunity in germ-free and antibiotic-treated mice. More studies will be required to investigate further whether bile acids regulate the functions of innate and adaptive immune cells in mice with experimentally altered composition of commensal bacteria.

Commensal bacteria–derived short-chain fatty acids

SCFAs are 1–6 carbons in length and are produced in the colon by bacterial fermentation of plant-derived nondigestible polysaccharides, such as cellulose (**Fig. 3a**)[76-79]. The most abundant SCFAs are butyrate (C4), propionate (C3) and acetate (C2) in the intestinal lumen[80,81]. Compared to the case in conventionally reared mice, the contents of colons of germ-free mice include more of the nondigestible plant oligosaccharide raffinose[40], a bacterial fermentation substrate[82], and markedly diminished concentrations of SCFAs[83-85], indicating that commensal microbiota are essential for synthesis of SCFAs.

SCFA regulation of immune cells

Several roles have been described for SCFAs, including the regulation of host metabolism[86-88] and function of the immune system[85,89,90]. SCFAs might regulate the immune system in multiple ways, for example, through the activation GPR43 (free fatty acid receptor 2, FFA2)[91-93], the inhibition of histone deacetylases[84,94-97] or the regulation of autophagy[84,98] (**Fig. 3b**). GPR43 is a G protein–coupled receptor that recognizes endogenous SCFA ligands, including acetate, propionate and butyrate[91-93,99], and is highly expressed in neutrophils, macrophages and monocytes[92,100]. A similar receptor, GPR41 (FFA3), also recognizes SCFA ligands with a different rank-order of ligand potency[91-93,99], but GPR41 expression is low or undetectable in neutrophils and monocytes[92,100], and at present there is limited evidence to suggest a direct role for GPR41 in the regulation of the immune system.

SCFAs propionate and acetate, derived from commensal bacteria, promote neutrophil chemotaxis[85,89,90,92]. The SCFA-induced chemotactic response in neutrophils is associated with an increase in intracellular calcium levels, a decrease in cAMP concentration and activation of ERK1/2 (ref. 92). Unlike bone marrow–derived neutrophils (BMDNs) from wild-type mice, Gpr43$^{-/-}$ BMDNs do not exhibit calcium influx in response to acetate treatment and do not undergo acetate-induced chemotaxis[85]. Furthermore, production of reactive oxygen species and the phagocytic activity of wild-type BMDNs but not of Gpr43$^{-/-}$ BMDNs is increased with acetate treatment[85], indicating that SCFAs promote not only neutrophil chemotaxis but also neutrophil function. Consistent with the role of SCFAs in promoting neutrophil chemotaxis, Gpr43$^{-/-}$ mice treated with DSS to induce colitis had lower neutrophil content in the colon compared to wild-type mice treated with DSS[89]. However, other studies report fewer colonic neutrophils in wild-type mice treated with DSS and acetate[85] or DSS and butyrate[101] compared to mice treated with DSS alone. It is not known why treatment with SCFAs and genetic deletion of the SCFA receptor GPR43 led to similar anti-inflammatory phenotypes in DSS-induced colitis, and further research will be required to investigate this issue.

Other cell types have also emerged as targets of SCFAs, including monocytes, dendritic cells, T cells and intestinal epithelial cells (**Fig. 3c**). Human peripheral blood mononuclear cells (PBMCs) express GPR43, and treatment of this cell type with SCFAs diminished expression of monocyte chemotactic protein-1 and production of TNF, IFN-γ and IL-10 in response to treatment with lipopolysac-charide[100]. In dendritic cells, treatment with butyrate is associated with decreased expression of the pro-inflammatory cytokines IL-12 and IFN-γ, and increased expression of IL-10 and IL-23 (refs. 102,103). There is also some evidence to suggest that butyrate may regulate the ability of dendritic cells to present antigen and to prime T cells. For example, butyrate treatment of dendritic cells is associated with downregulation of antigen-presentation machinery, including CD40, CD80, CD86 and major histocompatibility complex class II (refs. 102,103). In a dendritic cell and T cell co-culture system, however, butyrate-treated dendritic cells elicit increased T cell–derived production of IL-17 and IL-10 (ref. 102). In addition to regulating dendritic cell–T cell interactions, SCFAs might also directly regulate responses of T cells, as SCFAs may inhibit proliferation and promote apoptosis in CD4$^+$ T cells[104-107]. Furthermore, SCFAs appear to regulate production of proinflammatory cytokines in nonimmune cells, as Caco-2 cells treated with butyrate and IL-1β produce less IL-8 than do Caco-2 cells treated with IL-1β alone, indicating that a colonic epithelial cell line is also responsive to butyrate[108]. In primary colonic epithelial cells, SCFA deficiency establishes an energy-deprived state and leads to activation of autophagy[84], a process that is linked to many aspects of innate and adaptive immunity[98] and the maintenance of intestinal barrier integrity[109]. The molecular mechanisms by which SCFAs regulate all of these cell types are not well understood, although treating cells with butyrate has been linked to the inhibition of histone deacetylases[84,86,97,105,110] and alterations in histone acetylation that depend on the metabolic state of the cell[95]. Future studies will be required to define the full spectrum of cellular targets and molecular mechanisms through which SCFAs regulate development and function of immune cells.

SCFAs in health and disease

As discussed above, commensal bacteria are essential for the production of SCFAs, which appear to have anti-inflammatory properties in multiple types of immune cells. This raises fundamental questions about whether SCFAs might contribute to responses of immune cells in diseases associated with alterations in populations of commensal bacteria. Germ-free mice, which are deficient in SCFAs in the gastrointestinal tract[83-85], exhibit an exaggerated response of the immune system to DSS-induced colitis in some studies[85]. Consistent with these findings, treatment of germ-free mice with the SCFA acetate is sufficient to ameliorate the intestinal inflammation in response to treatment with DSS[85]. This effect is not observed in *Gpr43*$^{-/-}$ mice, indicating that GPR43 is required for the anti-inflammatory effects of SCFA in this model of intestinal inflammation in germ-free mice[85]. In contrast, another study showed that conventionally reared *Gpr43*$^{-/-}$ mice exhibit less intestinal inflammation in response to treatment with DSS than wild-type mice but develop systemic bacterial dissemination and die of complications resulting from sepsis[89], suggesting that SCFAs might regulate intestinal barrier function, a topic that warrants further investigation. Notably, treatment of IBD patients with butyrate enemas diminishes intestinal inflammation[111], and *in vitro* treatment of IBD lesional biopsies with butyrate is associated with lower production of pro-inflammatory cytokines[112]. Collectively, these studies suggest that SCFAs might influence responses of immune cells in at least some forms of IBD. Despite these advances, future work will be required to define how SCFAs regulate responses of the immune system in the context of IBD.

Commensal bacteria–derived vitamins and immunity

Vitamins are organic nutrients that are necessary for normal cellular function. For humans, there are 13 essential vitamins: the fat-soluble vitamins A, D, E and K and the water-soluble vitamins B_1, B_2, B_3, B_5, B_6, B_7, B_9, B_{12} and C. Some commensal bacterial species have the capacity to synthesize essential vitamins, especially of the B and K groups, and this has been proposed to be an important source of these vitamins[113]. The influence of vitamins on development and function of immune cells has been discussed in detail elsewhere[114-122], and we will therefore briefly discuss this here only in the context of a recently discovered link between commensal bacteria–derived vitamin biosynthetic intermediates and immune cells that directly recognize these intermediates. In particular, the monomorphic major histocompatibility complex class I–related protein (also known as MR1) presents vitamin from the riboflavin (vitamin B_2) biosynthetic pathway to mucosa-associated invariant T cells[122], a population of T cells that produces IL-17 and IFN-γ and that is activated in response to microbe-derived products of the riboflavin biosynthetic pathway[122-126]. These data suggest that commensal bacteria–derived metabolites in vitamin biosynthetic pathways, not just the vitamin end product, may be previously unappreciated groups of molecules that regulate immune cells or that immune cells use to sense commensal bacteria. Whether immune cells recognize intermediates of other vitamin biosynthetic pathways has yet to be determined. In addition, it is currently unknown whether or how vitamin biosynthetic intermediates influence development, homeostasis or function of immune cells—topics that should be the subject of future inquiries.

Commensal bacteria–derived amino acids and immunity

There are 20 essential amino acids that must be acquired through the diet and absorbed via amino acid transport proteins in the intestine. Several studies suggest that commensal bacteria are important for the extraction, synthesis or absorption of some amino acids, including alanine, aspartate, glutamate, glycine and tryptophan, although many of the reported differences in these amino acids appear to be tissue-specific[40,44,127-132]. Amino acids serve as building blocks for protein synthesis, substrates that feed directly into metabolic pathways (for example, glutamine into the citric acid cycle) and cell-to-cell signaling molecules (for example, the neurotransmitter glycine). Some amino acids, such as arginine, leucine, glutamine and tryptophan, are also associated with regulation of the immune system[119,130,133-140]. It is not yet known whether amino acids that are regulated by commensal bacteria influence the development, homeostasis or function of immune cells, but emerging research suggests that this might be the case. For example, tryptophan concentrations in the lumen of the colon are lower in germ-free mice compared to conventionally reared mice, suggesting that production or absorption of this amino acid is altered in the absence of commensal bacteria[131]. Tryptophan influences proliferation of T cells by regulating passage through the G1 phase of the cell cycle[137] and regulates immune responses in models of skin allo-graft rejection, tumor growth and autoimmune encephalomyelitis[138] as well as in TNBS-induced colitis[119]. Additional research is required to investigate the emerging link between amino acids that are regulated by commensal bacteria and the immune system.

Alterations in the composition of commensal bacteria could be an important etiologic factor in protein energy malnutrition (PEM)[127,128], a set of diseases characterized by immunodeficiency. For example, children with various forms of PEM have greater rates of infection[141-143], higher infection-associated mortality[143,144] and diminished vaccine efficacy[145,146]. Although insufficient dietary protein intake is considered to be a causal factor in the development of PEM, recent data suggest that commensal bacteria also have a role in PEM[127,128], perhaps because of their ability to synthesize, extract or regulate the absorption of amino acids. Supporting this hypothesis, it has been demonstrated that twins discordant for kwashiorkor, a PEM disease, have distinct gut microbiomes[127]. In addition, colonization of germ-free mice with fecal matter from the kwashiorkor-affected twin leads to rapid weight loss as well as impaired weight gain when given ready-to-use therapeutic food, a clinical intervention used in areas of widespread undernutrition[127]. Moreover, treatment of kwashiorkor patients with ready-to-use therapeutic food plus an oral antibiotic cocktail resulted in increased weight gain and decreased mortality compared to kwashiorkor patients treated with ready-to-use therapeutic food that did not receive antibiotics[128]. This suggests that commensal bacteria contribute to the etiology of this PEM disease, a notion supported by studies of germ-free mice that suggest that commensal bacteria regulate bioavailability and/or uptake of amino acids[40,44,129,131,132]. The mechanisms through which commensal bacteria regulate host amino acid metabolism in various compartments are unclear, and understanding how commensal bacteria-dependent amino acid abnormalities affect the immune system will require additional functional analyses.

Commensal bacteria, fatty acids and immunity

Fatty acids are a large family of nutrients that serve as energy substrates and that regulate or support the function of many immune cells. Germ-free fish, mice and rats exhibit altered lipid metabolism[3,5,40,41,44,147], and lipid homeostasis abnormalities in germ-free mice can be partially rescued by colonization with human fecal contents[39]. Furthermore, mice reared in a germ-free environment have lower fat mass compared to their conventionally reared counterparts[5], a phenotype that is associated with a diminished capacity for harvesting energy from ingested food[61] and a broadly altered lipid profile[5,40,41,44,147]. Commensal bacterial regulation of lipid homeostasis has also been reported in other species, as zebrafish raised in an axenic environment exhibit impaired lipid absorption and altered lipid profiles[3]. It therefore seems that commensal bacteria are necessary for the maintenance of lipid homeostasis.

This association raises the question of whether commensal bacteria regulate the immune system via modulation of systemic lipid homeostasis. Such a phenomenon could be mediated in at least two ways: the direct sensing of lipid moieties or the establishment of a metabolic program that favors some immune functions or the development of some cell types over others. The first mechanism is supported by data showing that invariant natural killer T (*iNKT*) cells, which recognize and respond to glycolipid antigens presented on the major histocompatibility complex class I–related molecule CD1d[148] are altered in mice lacking commensal bacteria[149,150]. Germ-free mice and a wild-type strain with less *Sphingomonas*, a glycolipid-producing commensal bacteria taxa, have fewer *iNKT* cells compared to wild-type mice harboring more *Sphingomonas*[150]. Others have shown that there are more *iNKT* cells in the small intestine of germ-free mice, a tissue-specific effect associated with signals derived from commensal bacteria early in mouse development that regulate the ontogeny of *iNKT* cells[150].

Commensal bacteria might also regulate immune cell function through the fatty acidy sensor proteins in the peroxisome proliferator-activated receptor (PPAR) family of nuclear receptors that recognize endogenous and exogenous lipid moieties and initiate transcriptional changes linked to metabolic reprogramming and immune function[151-155]. Commensal bacteria promote PPAR-γ–dependent export of NF-κB from the nucleus and decrease expression of the NF-κB–dependent gene *Il8* in a PPAR-γ–dependent manner[156]. Moreover, treatment of human intestinal epithelial cells from new-borns with *Enterococcus fecalis* is associated with the activation of PPAR-γ1 and increased production of IL-10 (ref. 157). Therefore, commensal bacteria appear capable of producing or stimulating the production of PPAR-activating molecules. However, additional research is needed to investigate the molecular mechanisms by which metabolites derived from commensal bacteria regulate PPAR family members and to explore how commensal bacteria regulate the immune system via PPARs.

An alternative mechanism by which alterations in lipid homeostasis can alter immune system function is by establishing a metabolic state that favors some immune processes over others. For example, T cells rely on fatty-acid oxidation at steady state and proceed through multiple metabolic checkpoints as they become activated, expand, contract and differentiate into effector or memory T cells[25,26,158]. T helper cells, including T_H1, T_H2 and T_H17 cells, tend to rely on glucose metabolism, whereas regulatory T cells and memory $CD8^+$ T cells exhibit increased fatty acid oxidation[27,28,159]. Blocking glycolysis inhibits development of T_H17 cells and promotes generation of T regulatory cells[28]. Treating mice with the anti-diabetes drug metformin or the immunosuppressant drug rapamycin, two pleiotropic molecules that promote oxidation of fatty acids via distinct pathways, is associated with increased $CD8^+$ memory T cell formation and function[159]. Oxidation of fatty acids also regulates hematopoietic stem cell maintenance and immune cell hematopoiesis[160]. Thus, the metabolic characteristics of immune cells may dictate their development and function, and alterations in lipid homeostasis that are dependent on commensal bacteria may represent an unappreciated mechanism through which commensal bacteria influence the immune system. Additional functional studies will be required to understand how lipids derived from commensal bacteria and alterations in host lipid homeostasis mediated by commensal bacteria regulate immune responses.

Conclusions and perspectives

In this Review we discussed how beneficial commensal bacteria in the gastrointestinal tract regulate the production of immunomodulatory, diet-dependent nutrients and metabolites. Commensal bacteria are required for the production of bile acids and SCFAs, both of which have anti-inflammatory properties in multiple immune cell populations. In addition, commensal bacteria are important sources of vitamins and amino acids and regulate systemic lipid homeostasis, and alterations in the levels of these metabolites can influence immune function. Although important advances have been made in our under-standing of the commensal bacteria–metabolite–immune system axis, fundamental gaps in knowledge remain regarding how nutrients and other metabolites derived from commensal bacteria regulate host metabolism and immunity. Future challenges include interrogation of the molecular mechanisms through which nutrients and metabolites derived from commensal bacteria regulate immune responses and linking the commensal bacteria–metabolite–immune system axis to human diseases that are associated with alterations in populations of intestinal commensal bacteria. Elaborating our understanding of the commensal bacteria–metabolite–immune system axis in the context of health and disease may provide useful insights for the development of improved preventive and therapeutic agents of multiple infectious, inflammatory and metabolic disorders.

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Box 1

Definitions

Metabolites; intermediates and products of metabolism. This is a broad term that usually refers to small molecules.

Nutrients; a subset of metabolites that must be acquired from the environment to support cellular processes. In mammals, the diet and commensal bacteria provide most nutrients[7-14].

Commensal bacteria; beneficial bacteria that reside on host barrier surfaces such as the intestine. Although the term ‘pcommensal’ implies that bacteria benefit and the host is unaffected, commensal bacteria and the host have a mutualistic relationship in which both derive benefit from the interaction[15].

Dysbiosis a state in which commensal bacteria populations are altered or imbalanced15. Dysbiosis is associated with several human diseases[45,58-68].

Diet-dependent microbial products: factors derived from commensal bacteria (for example, nutrients and metabolites) that are directly linked to diet or digestion[14]. Examples of diet-dependent microbial products include but are not limited to bile acids, short-chain fatty acids, vitamins, amino acids and fatty acids. The case of bile acids illustrates this concept. Commensal bacteria participate in the synthesis of bile acids, a family of metabolites that are stored in the gall bladder and secreted into the intestinal lumen in response to diet-dependent signals[32-45]. Bile salts then facilitate the digestion and absorption of lipids[32]. Therefore, bile acids derived from commensal bacteria are directly linked to both diet and digestion and can be considered to be diet-dependent microbial products.

Diet-independent microbial products: factors derived from commensal bacteria that are not directly linked to diet or digestion[14]. Examples include but are not limited to lipopolysaccharide and peptidoglycan.

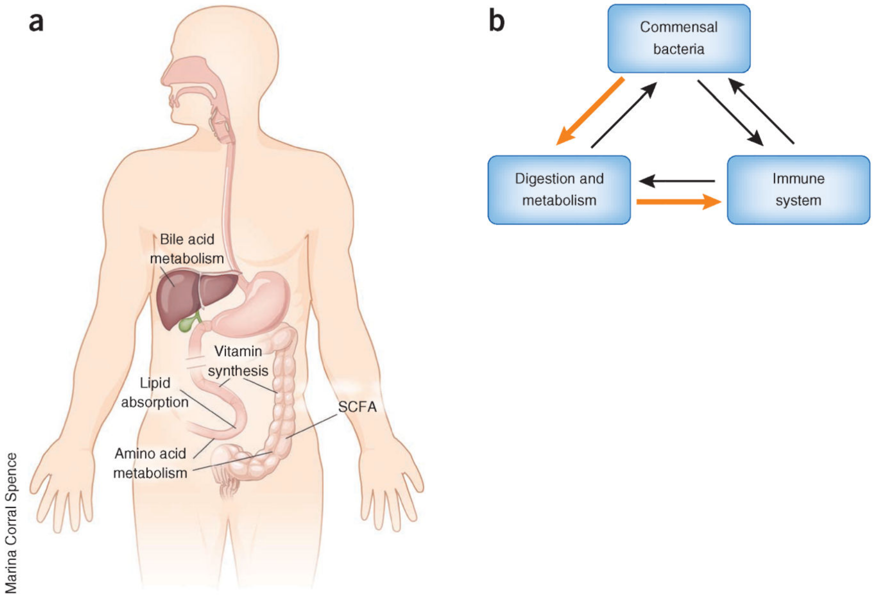

Figure 1.

Commensal bacteria at the interface of host metabolism and immunity. (a) Commensal bacteria regulate digestion by mediating bile acid synthesis, lipid absorption, amino acid metabolism, vitamin synthesis and SCFA production. (b) Commensal bacteria participate in digestion and regulate host metabolic homeostasis, and commensal bacteria–derived nutrients regulate the immune system. This commensal bacteria–metabolite–immune system axis (orange arrows) exists in a complex network of interactions among commensal bacteria, host digestion and the immune system (orange and black arrows).

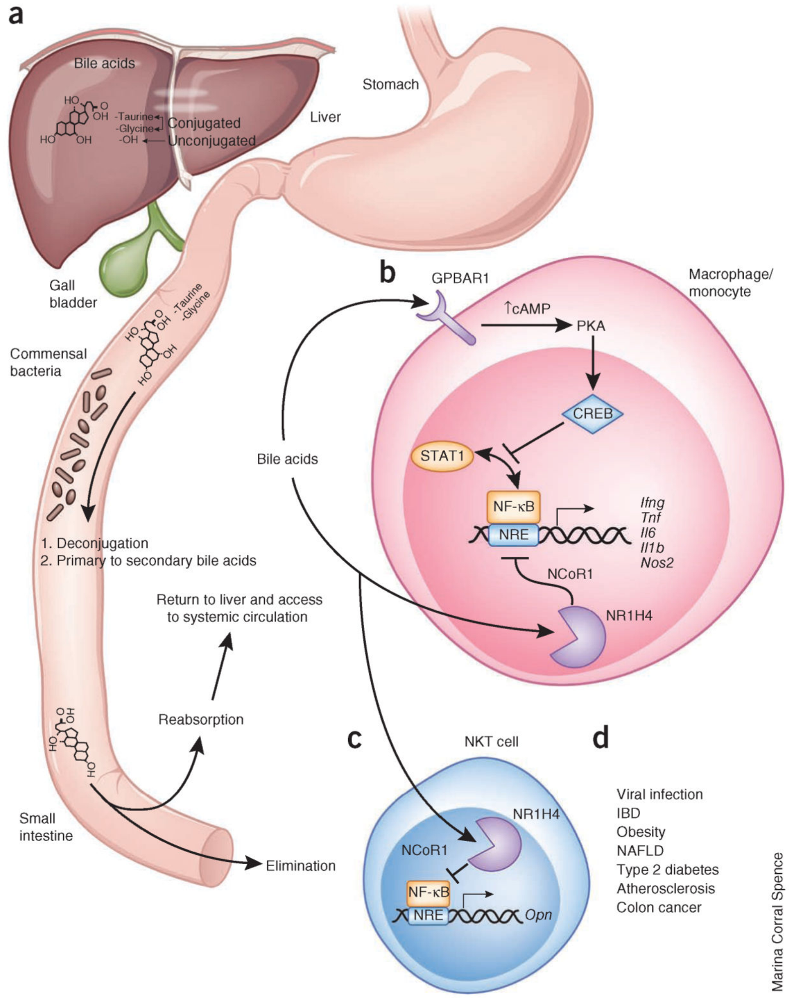

Figure 2.

Regulation of bile acid metabolism by commensal bacteria and effects of bile acids on immune cells. (a) Roles of commensal bacteria in synthesis of bile acids. Bile acids are synthesized in the liver from cholesterol-derived precursor molecules and are emptied into the small intestine. There, commensal bacteria deconjugate bile acids and convert primary into secondary bile acids. Bile acids are reabsorbed in the ileum and transported to the liver to complete enterohepatic circulation. Some bile acids gain access to systemic circulation. Molecular structure of bile acid is representative of some but not all bile acids. (b) Bile acid signaling in macrophages and monocytes via GPBAR1 and NR1H4. Both pathways lead to inhibition of NF-κB, albeit by different mechanisms. GPBAR1 signaling involves cAMP-PKA-mediated inhibition of STAT1 and NF-κB, and NR1H4 signaling leads to NR1H4-NCoR1–mediated repression of NF-κB–responsive elements (NRE). Bile acid stimulation of both pathways leads to less NF-κB–dependent gene expression. (c) Bile acid signaling in NKT cells. This cell type expresses NR1H4, and bile acid engagement of this nuclear receptor represses osteopontin expression. This molecule has many functions, including promoting neutrophil activation and chemotaxis as well as NKT cell activation in an autocrine or paracrine manner. (d) Pathogens and diseases associated with immune responses regulated by bile acids. NAFLD, non-alcoholic fatty liver disease.

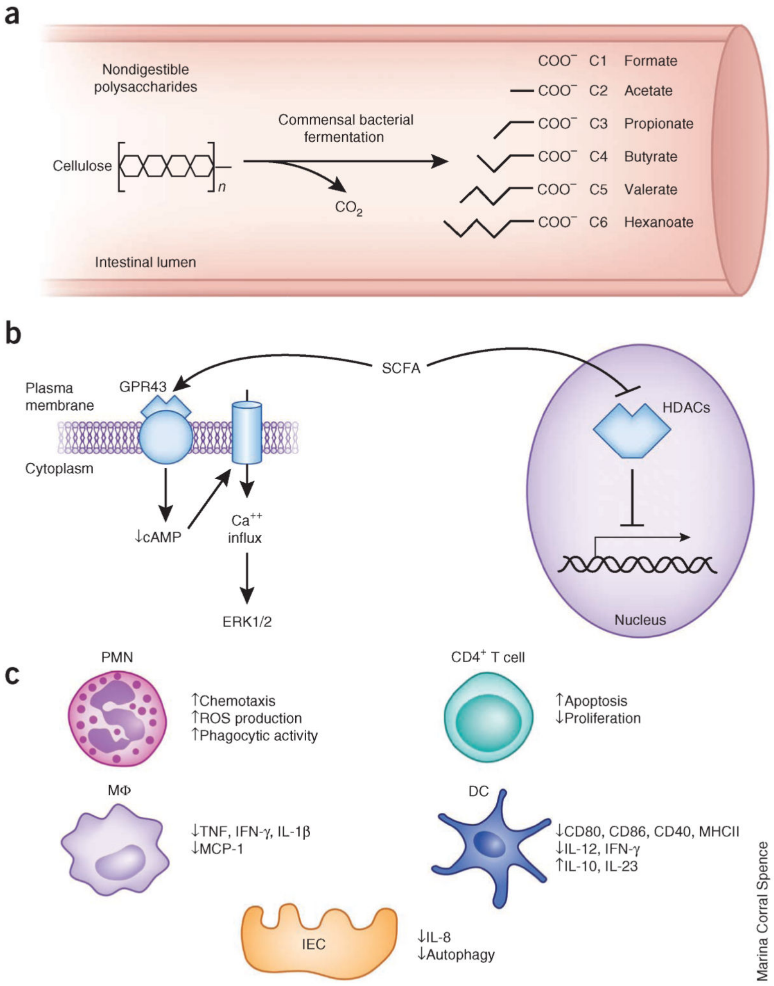

Figure 3.

Synthesis of SCFAs by commensal bacteria, and regulation of immunity by SCFAs. (a) Commensal bacteria ferment nondigestible polysaccharides ingested in the diet (for example, cellulose) to produce SCFAs. Various SCFAs and their molecular structures are shown. C1–C6 refers to the number of carbons. Isoforms of these SCFAs are not shown. (b) Known molecular pathways through which SCFA regulate populations of immune cells. SCFAs bind the G protein–coupled receptor GPR43, which leads to a decrease in cAMP levels, calcium influx and ERK1/2 activation. SCFAs also inhibit histone deacetylases (HDACs), which are transcriptional repressor proteins. (c) SCFA regulation of neutrophils, macrophages/ monocytes (MΦ), dendritic cells (DCs), $CD4^+$ T cells and intestinal epithelial cells (IEC). ROS, reactive oxygen species; MHCII, major histocompatibility class II.